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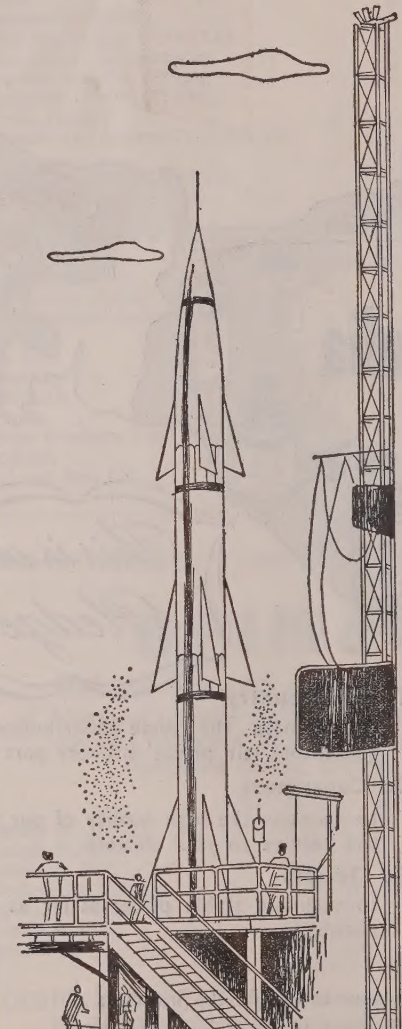

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Antibiotics Of Therapeutic Importance

"If the health of an individual goes wrong, the physical health of a nation goes wrong and it affects the world too."

—JAWAHARLAL NEHRU

TO those not familiar with the evolution of antibacterial chemotherapy it may be surprising that twenty-five years ago, when the clinician was confronted with a bacterial infection like pneumococcal pneumonia, staphylococcal sepsis or meningitis, he did not know what to do. The drugs at his disposal were not comparable in effectiveness to the ideal ones. "God cured the disease and the doctor had his fee." The position has, however, changed dramatically, after the advent of the sulpha drugs in 1935 and the antibiotics in 1940. As a result of tremendous amount of scientific man-power expended in the search for new antibiotics, nearly 600 antibiotics satisfying the definition of Waksman, have been discovered. After having gone through the mill of elaborate pharmacological and experimental testing in animals, about twenty of these have emerged as worthy of consideration for trial in human beings. From here to move on to the stage of a clinically essential antibiotic of the essential category is a step requiring lots of experimentation and selection. The average doctor has at his disposal such an array of antibiotics, with newer ones announced in his daily mail with attractive literature from the pharmaceutical houses, that he does not really know which is the antibiotic of choice for use in a particular case. Even the specialist is hard put to know and assess the ever expanding scientific literature.

In recommending the antibiotics for general use, many points have to be carefully considered. It should not be forgotten that the antibiotic is there for use solely for curing the patient of the illness in the quickest and best possible way. Next, for use in treatment as a routine, what is required is the best, cheapest and safest possible antibiotic. There is a wrong impression prevalent among some that the antibiotics that have come out in recent years are better than the older ones. In fact, the oldest of the useful antibiotics, penicillin, is still one of the best available and hard to replace. The wide use of the antibiotics gives rise to some problems of social and public health importance, such as the emergence of resistant forms of the pathogens or sensitisation of the patient to the antibiotic making him unfit for receiving the antibiotic in his system and thus restrict its use. Unfortunately, in these days of cut-throat commercialism and competition, the drug houses which have expended money in discovering some antibiotics are interested in pushing them into the market under some pretext or other, which has resulted in the use of some antibiotics which should not be in the market at all. The question now arises : which are the antibiotics that are essential for us from the general public point of view. A careful and critical survey of the subject leads us to the following conclusions.

PENICILLIN is still the most useful antibiotic, being extra-ordinarily useful in the treatment of infections due to almost all gram positive and gram negative cocci, gram positive bacilli and the spirochetes. It is, however, valueless in the treatment of infections due to the gram negative bacteria, rickettsiae, viruses, yeasts and fungi. Even today, about 40 per cent of all the antibiotics produced and sold constitute pencillin. PENICILLIN G is the one usually used mostly as the injection and there are many forms of it. The sodium and potassium salts are the water soluble injectable forms used where adequate blood levels of it are to be had fairly quickly. All over the world, the use of

the sodium salt has given place to the potassium salt which is as effective as the sodium salt therapeutically, and has, in addition, some distinct advantages in the manufacture, being more stable under packaging conditions than the sodium salt, particularly under the tropical conditions. The clinicians in our country are not probably aware of this; they would be doing the people and the Penicillin Factory a service if they would switch on to prescribing the POTASSIUM PENICILLIN in the place of SODIUM PENICILLIN. PROCAINE PENICILLIN is the other salt of great value which after injection gives adequate blood levels for about a day. The usual and popular clinical dose of 300,000 units of PROCAINE PENICILLIN with 100,000 units of the SODIUM or POTASSIUM PENICILLIN is a great advantage. Most of the penicillin used should be of this type. The penicillin salts which maintain blood concentrations much longer than absolutely essential would be more of a disadvantage because of the possible risks of sensitisation. It should be borne in mind that such a useful antibiotic like penicillin is likely to be used many times in the life of an individual and nothing should be done restricting or prohibiting its use in individual cases by indiscriminate use.

The advent of PENICILLIN V (free acid), POTASSIUM SALT and CALCIUM SALT), the oral and painless penicillin, should indeed be a boon as it has the great advantage of being taken by the mouth so that its use could infiltrate to areas where there is a paucity of doctors to administer drugs by injection. When properly used and in adequate dosages, it should easily replace in our country 30 to 40 per cent of the total quantity of penicillins used. But the easy way of administration should not reduce it to the level of a drug prescribed for each and every ailment along with any mixture and as a short-cut to diagnosis. Penicillin is not after all an absolutely harmless drug.

STREPTOMYCIN is the next antibiotic to come into use and it has a distinct place in the armamentarium of the clinician. It has a very useful action against the gram positive and gram negative bacteria, being particularly effective against tuberculosis. As it produces some effects on hearing and for other reasons, it is best reserved for the treatment of tuberculosis and some gram negative infections where absolutely essential. In certain cases, a synergistic combination with penicillin is useful, but the practice of using this combination as a routine against any bacteriologically undiagnosed infection is certainly an unhealthy practice. DIHYDROSTREPTOMYCIN was introduced with a claim that it is non-toxic, but this has not been substantiated for it shows toxic actions of a different type and affects hearing also. As the two produce toxic symptoms of different types, there is coming up a practice of using a half and half combination of them. These are not, however, absorbed after oral administration, and so have to be injected.

CHLORAMPHENICOL (CHLOROMYCETIN) is an antibiotic which is unique in the sense that it is the only one to be manufactured synthetically on a large scale. It is given orally and has a distinct place in the treatment of typhoid which is still claiming victims in our country. This is the first of the "broad spectrum" antibiotics, being useful against the gram positive and gram negative bacteria and also the rickettsiae.

The next important group of antibiotics constitute CHLORTETRACYCLINE (AUREOMYCIN), OXYTETRACYCLINE (TERRAMYCIN) and the parent compound, TETRACYCLINE. These are also "broad spectrum" antibiotics of great value in the treatment of infections due to the gram negative bacteria, and rickettsiae as well. They are structurally very closely related and resistance of a bacteria against one produces resistance against the others also. It is, therefore, very important that the best among these is actually used. Though they cannot be considered to be absolutely equivalent in therapeutic effectiveness quantitatively, it appears that TETRACYCLINE is the most

useful and also more widely used among these three antibiotics. TETRACYCLINES are administered mostly by mouth, though we have preparations available for injection in cases of emergency.

While the antibiotics just considered alone are of primary importance, there are others in the second line of defence. Though it may at first appear to be an attractive practice to use all the antibiotic weapons available in the fight against pathogenic micro-organism at the same time, a careful consideration would show that this would be poor strategy. The reason is that the capacity of the micro-organism for adaptation is very remarkable and this renders the antibiotics harmless against them under certain conditions. So we have to keep in reserve some antibiotics and use them prudently and only when absolutely essential. It is here that the subduing of commercial interest to the welfare of the people comes in.

We have a number of antibiotics of clinical value which act almost like penicillin and which certainly would have been used extensively, if penicillin was not discovered at all. These are the "macrolide" antibiotics, CARBOMYCIN, ERYTHROMYCIN, SPIRAMYCIN and OLEANDOMYCIN. All these show cross resistance, and resistance develops easily against them, so that if resistance develops against anyone, the rest of them would become useless. So there is a danger in using a less potent one in that by this the good ones also would be rendered useless. Of these mentioned, it has been established that ERYTHROMYCIN is the best. There is no case to use the others. But ERYTHROMYCIN must be reserved for use only in cases where penicillin cannot be used for some specific reasons. This is also the practice followed in Britain. One more antibiotic in this category is NOVOBIOCIN which acts against the staphylococci like penicillin but it also is best reserved to treat cases where penicillin cannot be used.

There is a group of polypeptide antibiotics produced by sporebearing bacteria, BACITRACIN, POLYMIXIN B and TYROTHRICIN. BACITRACIN acts like PENICILLIN. It is not absorbed by mouth and so has to be injected. Because it is not very safe for routine use it should be restricted to special cases and for topical applications. TYROTHRICIN is also to be used only topically being too toxic for systematic use. POLYMYXIN B comes in the same category. This is the only antibiotic of definite action against pyocyanase infection and has to be reserved for treating this infection only.

NEOMYCIN and VIOMYCIN act like STREPTOMYCIN. They are not absorbed by mouth and so should be injected. They do not possess the margin of safety for routine use and so should be tried only in special cases as an alternative to STREPTOMYCIN.

It could be seen that the above mentioned antibiotics in the second line of defence are of limited use. They cannot be used in mass campaigns or as a routine by clinicians who cannot keep the patients under close observation.

There are two anti-fungal antibiotics—NYSTATIN and AMPHOTERICIN B which are of value in tackling some fungal infections. Though not ideal, these are the best we have at our disposal to control some of the fungal infections. As yet we have to find effective and reliable antibiotics which could be used to control the virus infections and cancer.

There are some antibiotics like RISTOCETIN, STREPTOVARICIN and VANCOMYCIN which are being tried. We have to watch them for some more time to give an opinion. The new antibiotic, KANAMYCIN, seems to show definite promise as a supplement to PENICILLIN.

The interest of the public requires that we do not put into use each and every antibiotic discovered and appear promising in experimental trials. There shall be a definite case existing for its use, or, otherwise, there is likely to be more of harm than good to patients in the long run. The new antibiotics introduced should do something distinct which established ones cannot achieve.

Screening of Soils For Antibiotics

K. S. GOPALKRISHNAN, Ph.D.

A STRIKING fact that emerges out of a study of man's ageless effort to master his environment, is that he turned to explore Nature for cures of the ills inflicted on him by environment. Indeed, he searched the earth, among plants and minerals, to find the cures. Increasing knowledge of plants and animals lead to the establishment of the science of microbiology which has helped modern chemotherapy.

Around the turn of the last century, a few years after the famous discoveries of Pasteur establishing the microbial cause of disease, Gossio showed that a fungus—a species of *Penicillium* from soil—produced a substance which could inhibit the anthrax bacillus in the laboratory. Emmerich and Low, a few years later, carefully studied pyocyanase, perhaps the first antibiotic, highly effective against bacteria but produced by a soil bacterium. In the years that followed Paul Ehrlich introduced the concept of differential action of a modified toxic substance, as between the disease causing parasites and the host cells. These two cardinal features independently developed over a period of time, formed as it were, the basis of what might be rightly termed the Age of Antibiotics, starting with the dramatic discovery of penicillin by Fleming and tyrothricin by Dubos. At once these discoveries spawned enormous developments in microbiology and chemistry.

However, it was only with the discovery of streptomycin by the veteran soil microbiologist, Waksman, that the importance of systematic soil screening for the detection and identification of newer substances was fully realised. This greatly stimulated the organization of soil screening programmes for antibiotics in the various industrial and university laboratories initially in the United States to be followed soon in other countries.

Out of such carefully organized screening programmes with the sole purpose of finding newer antibiotics have emerged, chloramphenicol, chlortetracycline, oxytetracycline and a few others which are rapidly finding use in combating disease.

Out of over six hundred antibiotics thus discovered, only about twenty are clinically useful. But as professor Waksman often recalls, they had to examine 10,000 cultures before they could find a useful one producing streptomycin, each successful antibiotic thus indicating thousands of examined organisms with unsuccessful results.

It is a fascinating story but let us pause and see what is actually done in these laboratories where soils from all over the world are continuously being screened for newer organisms producing newer substances or known organisms for newer properties. The first step is the systematic collection of a large number of soils on a vast scale. In the words of Kane and coworkers soils "From Alaska to Australia, from the banks of the Amazon to the shores of the Ganges, from the swamps of Florida and the Swiss Alps collectors scraped up small portions of earth for mycological studies." The result of a systematic study of many soils was the discovery of oxytetracycline.

On receipt of the soil samples, each is carefully catalogued as to the source, date of collection and condition of the soil. Each of these is carefully analysed in a microbiological sense. Aqueous extracts of the collected soils are plated out on a variety of nutrient media. The condition of plating out could be varied to bring out

what the microbiologist is looking for. Thus, for example, if he is interested in bacteria he would have to use a different medium and conditions than if he were looking for fungi. Testing a drop of each soil extract on a variety of media permits the development of different types of organisms. Media, for instance, ideal for fungi are not suitable for detecting bacteria. The converse is equally true. Again while it is necessary to develop the colonies of the organisms it is also essential to restrict their growth to facilitate isolation of each for further study and for developing pure cultures. For this, excellent methods are available, like using dilute media, minimal media and chemicals which would permit growth but restrict development. It is thus possible to get a picture of the population pattern of the soil. For example, introducing a small quantity of acid in the plate in which the soil is analysed would discourage the development of most soil bacteria without affecting the growth of the filamentous fungi. Antibiotics themselves are successfully used in the medium to discourage bacterial contamination. Thus a standard combination of penicillin and streptomycin is used to prevent most of the soil bacteria from crowding the screening plates. Actinomycetes which have provided a number of broad spectrum antibiotics on the other hand, flourish better under neutral or alkaline conditions. Similarly by introducing special substances like sodium propionate, rose bengal and oxgall, it is possible to encourage the growth of desired organisms to the exclusion of others. Thus, at this stage itself, depending on what the investigator is looking for, it is generally possible to have a directional screening for the purpose of isolating an organism with a desired biochemical property. Indeed this might be carried out even when the soil is collected. In this way, Waksman and others have found a preponderance of some organisms in certain environmental conditions. In other words it is possible to look for habitats to collect certain types of organisms.

After the colonies of these varied organism have developed in petri plates, a transfer of each is made to a test tube containing sterile nutrients suspended in agar. Sterility is necessary to develop pure cultures of individual organisms. After a week's incubation, the colonies can be recognized. This period is only an approximation for the majority of microorganisms. There are of course the very fast ones and those which grow very slowly. Curiously enough, the tubercle bacillus, the cause of one of the persistently deadly diseases, is a slow grower on most of the media. It is rather fastidious in regard to the nutrients.

A week's incubation period is generally sufficient to provide inoculum for further testing and purifying. For testing, the spores of the organism are inoculated into suitable media in Erlenmeyer flasks. Concurrently, subtransfers are made in other tubes and petri plates for identification. The incubation period in the flasks varies. After this period, however, samples of the broth are withdrawn and tested against organisms for general antibiotic activity. A number of methods are available for this and they are called bioassays. In the first instance the broth samples are tested against a number of organisms representing different types to get an idea of the range of activity. This selective activity-range is technically called the antibiotic spectrum.

The broth can be taken either from shaken flasks or from stationary ones. In the latter case it would be called surface culture, the original method by which even penicillin was manufactured for some years. This method is now obsolete. All antibiotic screening is done only from shaken flask cultures except in the case of some bacterial antibiotics where the organisms are shy of growing in submerged cultures. In smaller laboratories, preliminary testing of the antibiotic activity is done on solid media in petri plates. The organism iso-

lated from soil is first grown on a suitable medium in the centre of a petri plate, and incubated for a week. Several test organisms are streaked starting from the margin of the original organism. This is again incubated to afford time for growth of the test organisms. Those sensitive to the metabolic activity of the original organism would be inhibited. Often organisms which show activity on solid media do not sustain it in liquid cultures. Such organisms are practically useless as antibiotic producers.

Vast and fascinating improvements in methodology of isolating desired organisms have been reported in recent years. One of them is an outstanding idea developed by Dr. Rene Dubos of the Rockefeller Institute for Medical Research, New York. This is based on the concept that wild type strains in soil are exposed to a large amount of countercurrent antagonisms, so that potentially useful ones are likely to be missed in screening. He developed the ingenious idea of introducing into the soil, organisms for which an antagonist is sought. Soil thus enriched might show the desired organism. Originally it would have gone undetected. Specific antagonists are more likely to be found by such methods than by general methods. In the laboratory also petri plates having the test organisms can be used for plating out soil extracts thus improving the chance of finding desired antagonists. Critical choice of a suitable assay organism is a prerequisite for successful antibiotic screening. General antibacterial activity might be detected by employing a sensitive organism like *Bacillus subtilis* and antifungal activity by *Candida albicans*. In seeking an antibiotic specific for a particular organism, the latter is logically the sole test organism. When inherent dangers in using such an organism compel the use of substitute, its limitations should be constantly kept in mind. A "suitable substitute" is really a misnomer.

While it seems impossible to judge which is the best method to isolate potentially important organisms, a few points bearing on the problem are :

1. Failure to use a medium correctly and properly made, can lead to non-detection of potential antibiotic producers.

2. Media used in cross streak and assays must be carefully chosen to bring out antibiosis clearly.

3. Temperature, length of incubation period and pH of all operations are important in as much as they profoundly influence the antibiotic producer and the assay organisms.

We have here at the Hindustan Antibiotics, a continuous screening of soils and testing of interesting antibiotic producers on a systematic basis. Indeed such programmes along with the development of better strains of known antibiotic producers is an indispensable part of any antibiotic manufacturing concern.

The comparatively few soil organisms which show possibilities in the preliminary tests are then grown in larger quantities of fermentation media with the objective of obtaining the active substance at least in an impure form. The aim now is to see if the substance is something new. At this stage most of the products already isolated are eliminated. A few that remain—a minute percentage of the original number—are grown in pilot tanks and recovery and purification studies are made. Extended animal studies to assess the degree of protection the substance can give in specific infections are then carried out alongside of toxicity studies. One is unusually fortunate if the proportion of the still interesting ones is more than one in a hundred thousand. The biblical saying that "Many are called but few are chosen" is so true that it summarizes the vast effort of thousands of investigators in the field all over the world.

Biochemistry of Penicillin Fermentation

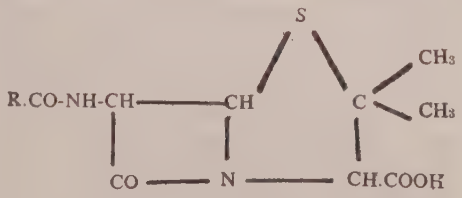
D. Ghosh, Ph.D. (Wis.)

Introduction

To-day, three decades after its discovery, penicillin is the most wanted medicine of the age, thanks to the team of researchers at the Sir William Dunn School of Pathology at Oxford University, who got curious in 1939 to initiate a systematic biochemical investigation on the production of anti-bacterial substances by micro-organisms. Bacteriolytic and bactericidal properties of microbial culture filtrates, various body fluids and tissues have, however, been known much earlier to Fleming's discovery of penicillin. Fleming himself called this enzyme-like lytic substance a "lysozyme" which was detected in blood, serum, plasma, tears, nasal mucous, saliva, etc., and also present in large amounts in egg white. Except for an unsuccessful attempt made in 1932 by Raistrick and others to isolate penicillin, apparently a very unstable compound, from a culture of Fleming's mould and a couple of reports in 1933 and 1940 confirming Fleming's observation and use of active culture broth as an aid in bacterial cultures, penicilling was for the time being practically dead to the scientific world. Professor Chain was earlier interested in the "lysozyme" and Fleming's mould and penicillin renewed his interest in bactericidal and bacteriolytic products of natural origin. Together with Professor Florey he cultured the mould and obtained a limited amount of impure penicillin for clinical trials. The story thereafter has been told and retold many times.

Development of Penicillin Fermentation

Penicillin (I), is the generic name for a group of closely related compounds synthesized by moulds of the *Penicillium notatum-chrysogenum* group under suitable biochemical environments. Entirely different groups of fungi are also capable of producing penicillin but *Penicillium chrysogenum* is now exclusively employed for



(I)

commercial penicillin fermentation. Until recently, pharmaceutical penicillin was entirely Penicillin G (Benzyl penicillin, R—C_6H_5. CH_2—). The mould is a versatile synthetic agent capable of substituting a large variety of organic acids as the R group under suitable conditions. Phenylacetic acid is employed in fermentation to give the benzyl group of Penicillin G. Substitution of phenylacetic acid with phenoxyacetic acid ($C_6H_5OCH_2COOH$) during fermentation gives rise to a new penicillin known as Penicillin V which is now on a large scale manufacture on account of its remarkable stability in acid solution and its usefulness in oral therapy.

During the very early days of penicillin manufacture by Anglo-American co-opera-

tion at the Northern Regional Research Laboratory, U. S. A., very little was known as to the chemical constitution of the penicillin molecule. For production, advantage was taken of earlier success and experience with gluconic, lactic and fumaric acid mould fermentation by submerged culture using corn-steep liquor and lactose as the principal sources of nitrogen and carbon. Corn-steep liquor is a by-product of maize industry and is practically a fermented product of the aqueous extract of maize in which sulphur dioxide is added to prevent putrefaction. It is very rich in amino acids, keto acids, fatty acids and trace nutrients like vitamins and minerals. With the Northern Regional Research Laboratory strain of *P. chrysogenum* (NRRL 1951) isolated from a mouldy cantaloupe, about 100 microgram per ml. of penicillin was produced in corn-steep lactose medium. It was estimated that a single batch of submerged fermentation in a 10,000 gallon tank would produce as much penicillin as could be obtained in 60 to 70 thousand milk bottles according to the original Oxford method of surface culture. This was a tremendous step forward in the technology of penicillin fermentation in 1943, but very little was yet known on the biochemical environment required for optimum growth of the mould and for penicillin formation.

The success in submerged fermentation clearly pointed out the importance of adequate aeration during metabolism and penicillin synthesis by this highly aerobic organism. In later years, extensive studies were made on the problem of aeration and oxygen diffusion into the mycelia in relation to optimum penicillin production. In commercial penicillin fermentation the empirically established practice is to bubble through the fermentation media as much as 0.7 to 1.0 volume of sterile air per minute throughout the course of fermentation lasting from 3 to 5 days. Although the theoretical requirements of oxygen is only about 5 per cent of the quantity actually provided by bubbling air, a number of physical factors peculiar to the design of the fermentor and physico-chemical conditions of the fermentation medium limit to a great extent the actual amount of oxygen available to the mould for oxidative metabolism after overcoming the interphasal barriers. Studies on respiratory metabolism of the fungus during penicillin fermentation is an important field for investigation.

Information regarding the successful use of corn-steep liquor and lactose in submerged fermentation of penicillin was not published until 1946 after the second world war. To-day this medium with certain modifications is in general use throughout the world.

After the initial technological success was achieved in submerged culture, research on penicillin fermentation proceeded along two main lines. First, strain development by selection and mutation in order to effect favourable changes in the genetic make-up of mould spores controlling the synthesis of vital enzyme systems responsible for penicillin biosynthesis. Second, biochemical studies on optimum nutrition environment for growth and penicillin synthesis by the fungus with which the present review is concerned.

Metabolic Aspects of Penicillin Fermentation

In present day commercial penicillin fermentation with improved strains and fermentation conditions the concentration of penicillin in the filtered broth at the end of fermentation ranges from 0.2 to 0.4 per cent or even more. This represents as much as 10 to 20 per cent of the total dry matter in the broth and the synthetic turnover is about 5 to 12 per cent of the total body weight of mould mycelia. Penicillin, therefore, can no longer be called a minor product of metabolism, although from a consideration of material

balance the yield of penicillin, unlike other fermentation products, e.g. citric acid, represents not more than 5 per cent of the total amount of nutrient raw materials.

Most of the published biochemical studies have been made in shake flask cultures and in pilot scale fermentors. In spite of the limitations of the applicability in large scale fermentations, laboratory results have provided invaluable information as to the optimum nutritional environment for penicillin formation by the mould.

In general, the course of penicillin fermentation can be characterized by three distinct metabolic phases. First, the period of rapid mycelial growth at the expense of readily assimilable carbon and nitrogen sources; rate of penicillin synthesis slowly increases with an initial lag period. Second, the period of slow mycelial growth and active penicillin production with a peak rate of synthesis; utilization of lactose runs almost parallel to penicillin formation. Finally, mycelial autolysis accompanied by little or no further increase in penicillin titre.

Mycelial Growth and Sugar Metabolism

Although good mycelial growth is the first essential, the amount of penicillin formed does not appear to be correlated with the amount of mycelia. Our observations that under identical fermentation conditions in large fermentors high yielding strains have high penicillin turnover per unit weight of mycelia are in conformity with earlier reports in shake flask fermentations with the strains Wisconsin 49-133 and 49-2105 which produced only about half as much mycelia as strains 47-1380 and 48-701 but gave considerably higher yields of penicillin. The nutritional problem here seems to be able to provide a sort of semi-starved condition so as to cut down unnecessary growth and divert the metabolic activity towards synthesis of products like penicillin which are non-essential for the growth of the organism. With the classical corn-steep-lactose media this condition of semi-starvation was readily achieved because lactose happened to be very slowly metabolised by the mould. The initial growth took place mainly at the expense of amino acids and lactic acids present in corn-steep liquor. In recent years studies at Wisconsin on this aspect of penicillin biochemistry demonstrated that the condition of semi-starvation could also be easily obtained by slowly and continuously feeding of cheaper and readily metabolizable sugars like glucose and ordinary cane sugar (sucrose) or even molasses. In laboratory experiments as well as in the factory we have also been able to replace the imported sugar lactose with ordinary cane sugar by suitable adjustment of slow feeding throughout the fermentation cycle.

Protein and Fat Metabolism

The mould *P. chrysogenum* is capable of utilizing other sources of nitrogen like peanut cake, mustard cake, cottonseed meal, etc., for penicillin production. Proteolytic enzymes are synthesized by the mould which steadily hydrolyse the complex protein molecules of the raw materials making available more and more readily utilizable amino acids. The mould is also capable of utilizing inorganic nitrogen sources like ammonium or nitrate ions for the synthesis of amino acids and proteins.

Experiments indicate that the waste mycelia filtered off at the end of the fermentation can also be utilized by the growing mould as the sole source of nitrogen for growth and penicillin production. Use of waste mycelia as one of the principal raw materials for penicillin fermentation appears to be an attractive proposition for a penicillin factory.

Penicillin fermentation medium contains animal or vegetable oils used as such or

as carriers of antifoam agents added to the medium to prevent foaming during fermentation. The mould has been found to synthesize lipase and secrete the enzyme into the broth as the fermentation progresses. This enzyme appears to play an important role in penicillin fermentation by liberating from oils fatty acids which not only provide readily assimilable carbon sources but also take part in the maintenance of optimum fermentation conditions with regard to pH and foaming. Some of the fatty acids like oleic acid commonly present in large quantities in vegetable oils have been reported to stimulate as well as inhibit penicillin biosynthesis depending upon the concentration used. A judicial use of oil in combating foam or regulating pH is of crucial importance in penicillin fermentation.

Mineral Metabolism

Requirement of minerals such as potassium, magnesium, phosphorus, iron, sulphur, copper, zinc, and manganese for optimum growth of and penicillin biosynthesis by, the mould have been studied. Natural fermentation medium generally contains enough of these minerals. However, to ensure adequate supply the medium is generally supplemented with mineral salts. The mould can use both inorganic and organic sulphur for incorporation of the sulphur atom in the penicillin molecule.

Our observations in factory scale fermentation indicate high rate of uptake of inorganic phosphorus from the media during the earlier part of the cycle when the respiratory activity is also very high.

Mechanism of Penicillin Biosynthesis

Studies with radioactive isotopes have clearly established that the complex penicillin molecule is synthesized by the mould from relatively simple compounds such as organic acid for the R side chain (see I), and the amino acids L-cysteine and valine for the ring structure. But the exact mechanism by which the amino acids constitute the closed structure is not yet clearly understood. For Penicillin G one single discovery that the benzyl group of the side chain can be furnished most effectively by feeding phenylacetic acid into the medium has been responsible for increasing the Penicillin G production several folds. Although the mould is capable of converting the amino acid phenylalanine into phenylacetic acid, neither the quantity of phenylalanine available in the media nor the rate of its conversion is high enough for an adequate supply of the precursor. The precursor value of added phenylacetic acid is thus fully utilized in industry. As mentioned earlier a large variety of organic acids could be fed during fermentation and with surprising ability the mould would incorporate the corresponding R side chain into the penicillin molecule.

The other two precursors cysteine and valine or their close derivatives are not rate-limiting in penicillin biosynthesis. As such during fermentation. However, fundamental studies on penicillin biosynthesis has made such remarkable progress in recent years that it may be possible soon to control the production of penicillin by fermentation with utmost biochemical precision in order to speed up the rate and amount of penicillin production.

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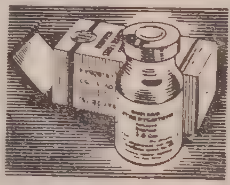

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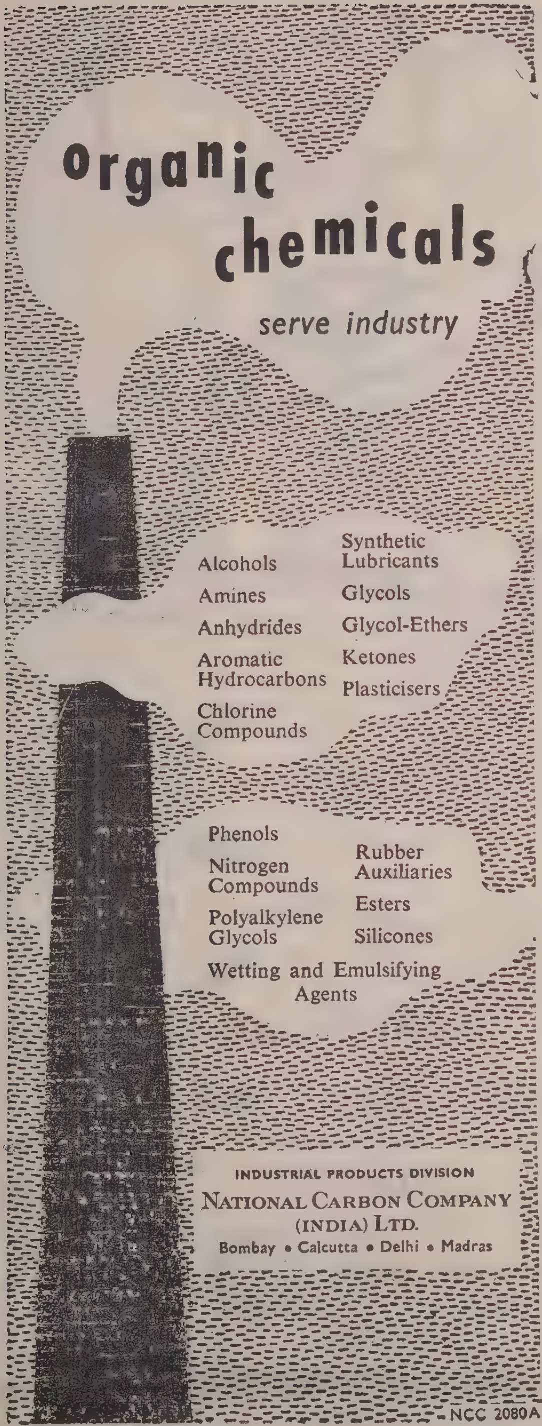
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Some Aspects of Toxic Hazards in Penicillin Manufacture

Dr. (Miss) I. K. Madhekar, M.B.,B.S.

STUDY of the effect of chemical agents upon health in an industry has, until recently, been confined almost exclusively to those aspects incidental to medico-legal problems. The physiological action, short of tissue injury, of these agents has received little attention. Bitter industrial experience, mainly gained during the last two world wars, has led to the realization that significant alterations in physiological conditions can occur before pathological lesions manifest themselves. The growing knowledge of the untoward effects of chemicals and the constant search for and institution of, appropriate preventive measures have minimized the risk to workers in general. Under industrial conditions when a worker or a group of workers manifest certain symptoms, it is difficult to ascertain whether they are due to the effect of the working environment and if so, which particular agent is responsible for this.

Absorption and Fate of Chemicals

The most important route of absorption of chemicals is through the lungs presented to it as dusts, fumes, mists, vapours or gases. From the lungs, the agent is carried to every part of the body by the circulating blood. Most of the volatile chemical is quickly eliminated chiefly in the expired air, and a certain amount in the urine. A small amount remains in the body, part of which may be stored unchanged, while portions may be converted to other chemical products which exert their own toxic effects either on the organs of storage, especially the liver, or on the organs of excretion. An important point is that a given atmospheric concentration of a toxic gas may be innocuous to a man sitting at a desk, but dangerous to the same man when engaged in physical labour which increases his rate and depth of respiration and his pulmonary blood circulation rate.

Absorption through the skin is possible in the case of water or fat soluble substances. Skin is not such a good protecting barrier as might be supposed. Wearing of contaminated clothing during and out of work hours, especially during periods of high temperature and humidity, can be as great a source of injury to health by non-volatile materials as is exposure to the vapours of volatile compounds.

The greatest exposure occurs among those who handle concentrated chemicals. Inhalation of fumes or vapours, and contact with splashes which might occur when opening or pouring the chemicals from the containers, are quite dangerous.

From an industrial point of view absorption through the digestive tract is more of an accident rather than a regular exposure hazard. However, part of the material entering the upper respiratory tract may be dissolved in mucous secretions or saliva and swallowed.

Nature of Toxic Actions

The toxic action of chemical agents is of two types. First, an individual may show toxic effects, acute or chronic, due to exposure to toxic doses. Even if there is a standard toxic dose of each chemical which

is applicable to the majority, there is individual variation in the susceptibility of a few individuals, some being less and others more susceptible than the majority. It is of interest to note that even if a chemical has specific action on certain organs, the general symptoms are very similar in all cases both in acute and chronic poisoning. It has been stated that symptoms correspond to those observed in Selye's "adaptation syndrome" which is "the sum of all non-specific systemic reactions of the body which ensue upon long continued exposure to stress." Second, a person may show hypersensitivity or allergy to a drug. In many cases, it is difficult or impossible to classify them definitely into allergic and non-allergic reactions.

Toxicity of Individual Chemicals

Pharmacologically penicillin is comparatively an inert substance and hence relatively harmless even in large doses. Untoward reactions to penicillin are mostly due to allergy. The allergic reactions may manifest as contact dermatitis, urticaria, periorbital or labial oedema, stomatitis, swelling or dermatitis of eyelids and the region below eyes, pruritus, oedema of the hands, headache and asthmatic attacks. In some workers, melanoglossia, *i.e.* black tongue, develops which may be related to an effect of the antibiotic on the flora of oropharynx or penicillin may be exerting a cornifying effect on the epithelium. Vigliani has reported that thiamine, niacin, and vitamin P help prevent black tongue. There are very few reported instances in which a worker had to leave his or her job because of sensitization to penicillin. In a factory exposure to penicillin occurs during its removal from centrifuges, traying and packing, its transfer from canisters to blender, loading the hopper, making solution of penicillin for procaine penicillin precipitation, milling or micronizing of penicillin salts, emptying discarded vials into salvage powder, and cleaning of Kilner jars.

SOLVENTS

Solvents commonly used in the manufacture of penicillin are acetone, butyl acetate and/or amyl acetate, butyl alcohol and isopropyl alcohol. Most observations on the toxic effects of solvents have been made with little direct relation to industrial conditions. Quantitative data on the physiological effects of solvent vapour is both scanty and in many instances conflicting. It is usual to prescribe a maximum allowable concentration of dust, gas, fume or vapour in which men may work without ill effects. The purpose of prescribing such concentration limits is to provide figures for guidance in routine industrial control of health hazards but mere maintenance of this concentration does not necessarily guarantee protection against ill health of a worker.

Goldblatts figures for concentrations of solvents required to produce different degrees of toxicity and maximum allowable concentrations are given in the table below:—

Solvent	Conc. causing severe toxic effects in persons exposed for the stated times			Conc. which if exposure continues for more than a short time may lead to symptoms of illness		Conc. in general atmosphere of plant greater than those below indicate unsatisfactory conditions	
	p.p.m. v/v	mg/cu metre 20°C	Time of exposure in mins.	p.p.m. v/v	mg/cu metre 20°C	p.p.m. v/v	mg/cu metre 20°C
Acetone	4000	9650	60	300	1930	400	965
Isoamyl-acetate	1000	5410	60	300	1623	100	541
n-butyl-acetate	2000	9650	60	500	2412	200	965
n-butyl-alcohol	1000	3080	60	100	308	50	154

Apart from their toxic action these solvents present a risk of explosion as they become highly inflammable when mixed with air in certain proportions.

Acetone.—Acetone is a highly volatile and inflammable liquid with narcotic and local irritant action. Its narcotic effect may not be observed in concentrations found in the industry. Symptoms of acute poisoning are nausea, vomiting and fainting, collapse and unconsciousness. There is no permanent injury to the body after recovery. Chronic poisoning gives rise to sensation of heat, giddiness, vertigo, headache, irritation of the throat and eyes, coughing and fainting attacks. Baldi reports irritant action on mucosa *e.g.* constant conjunctival irritation with reddening and lacrymation even below maximum allowable concentration. There may be irritation of corneal epithelium and some cases of leucocytosis and eosinophilia have been recorded. Loss of judgement and concentration may increase the likelihood of accidents. Parmeggiani and Sarsi have reported gastric pain, nervousness and insomnia. Because of its fat dissolving properties, sebaceous layer of skin disappears leading to diminished resistance favouring dermatitis. Exposure to acetone occurs during its transfer from the drums to the centrifuges, during the crystallization operations and drying of certain apparatuses.

Amyl acetate.—This is a volatile, inflammable liquid. Acute toxic effects include sensation of heat, giddiness, drowsiness, fatigue, tachycardia, irritation of the eye, nose and throat. Chronic toxic effects are headache, irritation of throat, cough, and feeling of oppression in the chest. Occasionally difficulty in breathing may occur during the first period of exposure to amyl acetate but these symptoms are transitory. Irritation of eyes is reported but it is not certain whether the conjunctivitis is specifically due to amyl acetate. Rarely digestive disturbances appear. Gutierrez de Alles has reported cases with pathological changes in ovaries, testes, thyroid and pituitary leading to sterility, in his study of 700 industrial workers exposed to benzene, ether, alcohol, ethyl acetate and amyl acetate. Exposure to amyl or butyl acetates occurs at various stages of handling during extraction and crystallization operations.

Butyl acetate.—This is 25 per cent more volatile and said to be less toxic, than amyl acetate with symptoms of acute toxicity similar to those of the latter. Chronic toxicity symptoms observed by various workers are conjunctival irritation, bronchial catarrh, headache, fatigue, feeling of oppression in the chest and gastric disturbances. Cases of liver damage have also been reported. But in most instances the solvent was used in combination with other chemicals so that the exact causative factor is not known for certain. Butyl acetate may also cause dermatitis.

n-*Butyl alcohol.*—Acute toxic effects are irritation of nose, throat and eyes, headache, drowsiness and giddiness. In chronic poisoning eyes are affected leading to conjunctivitis and keratitis. Symptoms and signs may be more prominent on awakening in the morning than during the day. The cornea may show minute transparent areas. Dermatitis of fingers and fissures around nails, fatigue, headache, vertigo and drowsiness are also noted. Liver damage has been reported where this chemical was used along with others, but the particular offending agent has not been found out. Exposure occurs while transferring the alcohol to centrifuges and mixing it with the penicillin crystals.

iso*Propyl alcohol.*—It is a mild irritant of the eyes, nose and throat and may induce mild narcosis. No ill effects are observed by its use undiluted as a disinfectant for the skin. Workers engaged in its manufacture are reported to have suffered from cancer of the nose and upper respiratory passages. The carcinogenic agent is not known. Exposure occurs while mixing isopropyl alcohol with penicillin powder and in its use as a disinfectant for the hands.

Acids, Alkalies and Alkaline Salts

Acids used in the penicillin industry are sulphuric and phosphoric acids; alkali and alkaline salts are sodium hydroxide, sodium carbonate, potassium carbonate and potassium acetate. Sulphuric acid is a highly caustic agent. If it falls on a large area of the skin there may be shock and collapse. Only dilute acid is used in penicillin manufacture. It acts as a mild irritant and workers are not liable to come in contact with it as it is transferred to the extraction section automatically through pipes. However, there are chances of accident if there is leakage.

Phosphoric acid is less irritant, causing redness and blistering when applied in concentrated solution. Contact is likely only where it is not transferred automatically and in case of leakage.

Alkaline salts also act as caustic agents. The solutions of carbonates are much less corrosive than those of hydrates and may induce actual lesions of the skin only under exceptional circumstances. Sodium hydroxide and alkaline salts are handled manually. Potassium salts have given rise to allergic reaction in the form of dermatitis in at least one worker at Hindustan Antibiotics.

Antifoams

Octadecanol or stearyl alcohol which is used as an antifoam has very low toxicity.

Disinfectants and Sterilizing Agents

The disinfectants usually used are propylene glycol, Pemon, formalin, isopropyl alcohol and ultraviolet rays.

Propylene glycol used for the disinfection of air has not been observed to produce ill effects. Pemon is also a harmless agent. Formalin vapour is highly irritating to the eyes and respiratory tract, and in contact with the skin may produce dermatitis.

The severity of the ill effects due to ultraviolet radiations varies according to the length of time the surface is exposed to them. First degree burn in the form of redness of skin may result from a relatively short exposure, the eyes exhibiting irritation of the conjunctiva, pain and photophobia. Degenerative changes of the skin leading to cancer have been noted with prolonged exposures to ultraviolet light.

Exposure to ultraviolet radiation occurs in the airlock of the sterile area where the worker changes into sterile clothes.

Ozone is produced in the vicinity of ultraviolet lamps. It is irritant to respiratory membranes. Nitrogen oxide which almost always accompanies ozone, may further aggravate the local irritation. Inhalation of 2-3 parts per million causes drowsiness and headache. Stockinger has reported pulmonary oedema and haemorrhage with high concentrations, while low concentrations have general depressant effect producing sleep in certain individuals. Maximum allowable concentration is near or below the minimum at which ozone can be detected by odour (0.05-0.1 ppm). Exposure periods of 3-4 hours/week to 0.1 ppm have been reported to produce symptoms of chronic poisoning after two weeks, *e.g.* shortness of breath and continuous headache.

Control of Hazards

The one important part of any industrial hazards control programme is that workers handling toxic materials should be aware of the dangers and be able to appreciate the significance of a warning. Ignorance, carelessness and disregard for human safety rules or instructions, are causes of most hazards. It should be ensured that the workers observe the recommended safety rules.

Remedial measures for preventing toxic hazards instituted in Hindustan Antibiotics are:

1. Efficient ventilation system with capacity for air changes at proper rates.

2. Equipment which are likely to give off large concentrations of vapour are provided with air jet ejectors to purge the vapours.
3. Closed methods of transport of chemicals as far as possible.
4. Regular rotation of operating personnel between subsections.
5. Half a seer of milk issued to each person working in closed areas.
6. Provision of goggles for the protection of eyes and clothing to cover the entire body for workers exposed to ultraviolet radiation.
7. Studies of concentration of solvent vapour to ascertain whether it is within safe limits.

To provide safe working conditions to the employees, it is essential to study the ill effects produced on their health by the working environment. The knowledge of toxic hazards is far from complete and as new chemicals are being added to the industry, every industrial concern should have a team consisting of the medical officer and representatives from the different sections of the factory, to observe ill effect and suggest modifications in the offending mechanism to prevent recurrence of the hazards.

The shadows are deepest

Where there is much light, the shadows are deepest, runs a proverb. And how quickly the source of light burns out, we may add !

You may find high tempo of living quite enjoyable while it lasts; but you use up a lot more energy you never have time to replace. Warning signals soon appear that bring gloomy shadows into your life. Don't ignore these warnings. Only your doctor is competent to probe into this darkness to set matters right. Obey his instructions. At the first sign...

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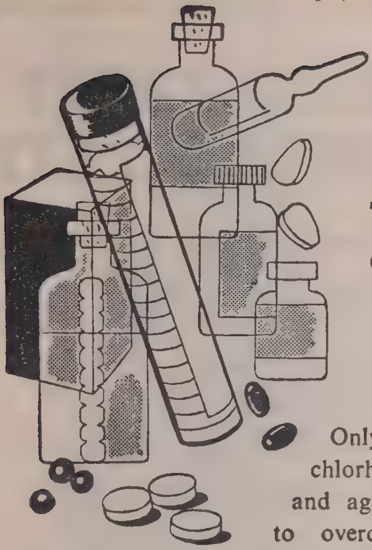

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... especially for the dyspeptic

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Training of Supervisors in Human Relations

K. C. SHAH, M.Com.

THE progressive industrialization of our country in general and the achievement of the targets under the Second Five-Year Plan in particular, require a very large number of trained personnel at the middle-management level. For the men entrusted with such managerial responsibilities, adequate training in the techniques of supervision and the psychology of human relations, are of vital importance. It is to be admitted that much of the dissatisfaction among workers in the public as well as private sector factories arises not merely from low wages or unsatisfactory working conditions but also from the treatment meted out by the supervisory personnel. The proper training of the personnel in middle-management level in human relations and in the psychology of supervision are, therefore, essential for the smooth progress and successful completion of our industrial plans and projects.

To the average workman, the supervisor with whom he comes in contact throughout the day and day after day, personifies the Company itself. The organization will, therefore, be judged by the worker largely on the kind of treatment he receives at the hands of the supervisor. It is, perhaps, needless to add that during the period when the new recruit learns his job, and gets accustomed to and tries to settle down in his new environments, the relationship that develops between him and his supervisor, can make all the difference between success and failure.

Techniques of Supervision

In training supervisors, it is necessary to impress upon them that they should put themselves in the shoes of the workmen and see their side of the situation. Of course, this may be difficult in every circumstance because supervisors are busy people, have to make quick decisions and such decisions may affect a number of workers if not the entire workforce. However, in personnel administration, the supervisor should view the question from every side—and this fundamental approach must be impressed upon all those at the middle management level including group leaders, operators, chargemen, foremen, etc., because, in the final analysis they are responsible for carrying out the personnel programme of the organization at various levels.

The supervisor who believes that he represents the company to the worker and tries to accommodate the views from the workman's side, is making a serious effort in the right direction to command, rather than demand, the respect of the employees. Bossing over and demanding implicit obedience and respect are bound to fail in the long run. To quote an instance from an organization I had served earlier, an Assistant Engineer asked one of his fitters to complete a particular job before the end of the shift. The work was too technical and complicated for the fitter and he could not complete it in time. Realising the nature of the work and looking at it from the side of the fitter,

the Assistant Engineer jokingly remarked that it would be necessary to carry the work home with him for completion. This set the fitter at ease and made for greater respect for the engineer.

Qualities Necessary in a Supervisor

The good supervisor acts not in the capacity of a boss but rather in the capacity of a leader of the workmen. A workman is likely to be more familiar with his job than anyone else and as such the supervisor should try to seek his advice and opinion on matters connected with that job. The supervisor can enlist better cooperation from his workmen by sharing a secret with them and by keeping them informed of the proposed changes in job methods than by keeping from them such information. The supervisor should always bear in mind that the workman whether he is skilled, semi-skilled or unskilled, is a human being and has his own feelings. The experienced and skilful supervisor would request rather than order a job to be done. This manner of approach is particularly important in the case of the new recruit who has something to suggest to the more experienced worker. The friendly approach ensures co-operation and better human relations. Considerable importance is given to the tone of the voice and the manner of speech of the supervisor. The successful supervisor makes the jobs which he wants to be done, look so attractive to the worker that the latter takes it up with pleasure. He also gives him a feeling of sharing in a mighty adventure of national production.

Infusing Self-pride in Employees' Work

Employees generally have great sense of personal pride in their work as much as the independent businessman or lawyer, and any method that the supervisor can use to develop and maintain this pride and dignity of labour, will promote interest and satisfaction in all concerned. The Managing Director or the head of the department who walks down to the plant, addresses the worker by his name and enquires of him about the various operations, creates a sense of satisfaction and jubilation in the workmen. An occasional enquiry about his family and general welfare also establishes a personal bond of loyalty and affection to the top man.

Handling the Defaulter

Indicating the proper methods of handling defaulters is an important part of the training in the psychology of supervision. Before awarding punishment the following three important points should be kept in mind:

Firstly, investigation and ascertainment of the facts of the case, and if this reveals a genuine excuse for committing an error, the defaulter should not be punished. Secondly, the worker should be given every opportunity to explain. Thirdly, a worker frequently has no chance to express himself and a minor matter may swell to a major grievance. The supervisor should remain calm while discussing the matters with the worker and should not "shout at" him, as this would only complicate matters. The method of "cooling off" is often the best way of punishment. When all these steps have been taken and it is found that the fault lies with the worker and therefore, punishment is necessary, the order of such punishment should be issued privately to the worker so as not to injure his pride and to preserve his respect for the supervisor. It is also necessary that the nature and degree of punishment should be arrived at impersonally without prejudice and more with a desire to correct rather than condemn.

Credit for Good Work

A few words of praise to workers pave the way for satisfactory results in building up morale. Everyone likes to be complimented for doing a good job, and therefore giving credit, recognition and praise where

they are due, makes for greater efficiency and better relations among the workers.

The supervisory staff is expected to know something about social security legislation and labour laws current in the country. The supervisor should not promise things which he cannot fulfil, for promises unaccomplished result in disappointment for the workers, lowering of morale, and even quitting of job by some of them. The supervisor should think twice before making any promises regarding transfers, promotions and such matters affecting workers unless he has the power to implement such promises. In a big concern, it happens that when workers put up a question concerning them, the supervisor will say "it is against the company's policy," but he should realise that this is an unsatisfactory answer as the employees would naturally like to know what such policy is and what are the reasons therefor.

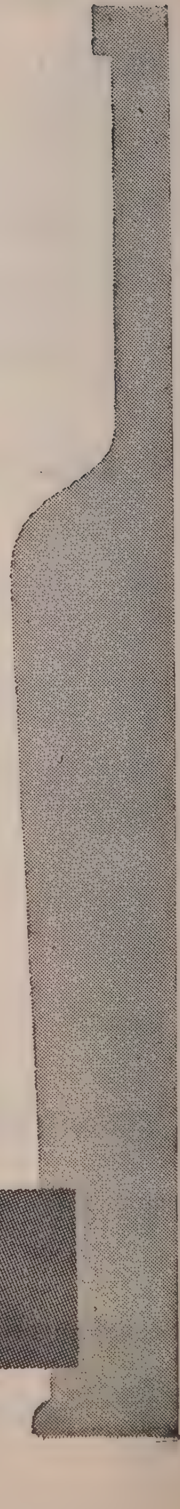
Handling Grievances

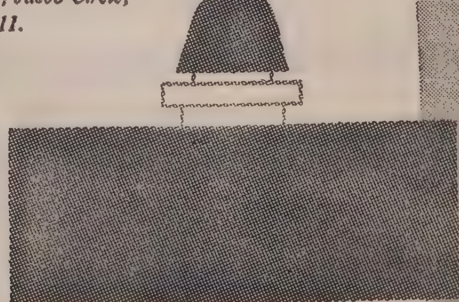
Wherever a number of people work together, feelings of personal injustice and wrongs under certain circumstances are bound to arise. Industrial organizations are so big today that the common workman finds little opportunity to communicate with the superior or with the management. He should however be given ample opportunities and freedom to present his case to the management and have his grievances settled. Present day labour laws have laid down that grievances of small nature should be settled through Welfare Officers appointed under the Factories Act. Fortunately, there is much closer contact these days between the Management and Labour than hitherto and each worker feels free to ventilate his grievances direct to the Management.

Maintenance of Discipline

The supervisor who has to command respect and be the leader of his men, must be able to maintain good discipline. He should be absolutely impartial in the administration of the Company's rules and regulations, should follow the orders, and should be able to judge whether persons working under him are entitled for praise or otherwise. A department where workers fail to do their job properly and where such negligence and shirking of responsibility go unpunished, is bound to go down in efficiency and discipline ultimately damaging the company and also the worker. Both praise and criticism should be expressed judiciously and at the right time.

An effort has been made in this short space to summarize some of the essential principles of supervision which may be adopted without much difficulty by persons at the middle management level. These principles are based on experience and are applicable to common problems of day-to-day administration and supervision. However, in order to implement effectively these principles in practice, the supervisors need adequate training. This "Training within Industry" is training in human relations so vital not only for a substantial increase in satisfaction and improvement of the efficiency of our workers, but also indispensable for the success of our industrial plans.





Antibiotics Information

Trends in Antibiotics Production

(II)[1] UNITED KINGDOM & WESTERN EUROPE

United Kingdom

The United Kingdom, besides being one of the pioneers in the field, is to-day the largest producer of antibiotics outside the United States and the U.S.S.R. Penicillin production has steadily increased except for a slight drop in 1955. Even in that year, sale of the antibiotic was up by 30 m.m.u. over 1954 figures. In 1955 streptomycin production was eight times that in 1950 and 50 per cent higher than in 1954; a further 6 per cent rise was registered in 1956. The National Health Service (NHS) purchases of antibiotics in 1956 was around £1.22 million (£1.4 million in 1955) out of a total of £8.5 million of medical supplies. There are over half a dozen important British manufacturers of antibiotics most of whom have subsidiaries and sales facilities abroad. The specialized antibiotics purchased by NHS came from 15 firms in 1957.

TABLE I

U. K. Production And Export Of Antibiotics[2]

Year	Penicillin production m.m.u.	EXPORTS					
		Penicillin			Value in million £		
		Quantity m.m.u	Value in million £		Other antibiotics	All antibiotics	All drugs and medicinals
			All penicillin preparations	Penicillin salts			
1945	0.36	—	—	—	—	—	6.4
1946	3.1	—	—	—	—	—	12.8
1947	4.9	1.7	1.1[3]	—	—	—	14.6
1948	9.7	4.3	2.07	2.05[3]	—	—	15.8
1949	18.6	7.6	2.6	2.5[3]	—	—	18.4
1950	37.6	13.7	3.8	2.8	—	—	23.1
1951	61.2	26.7	6.8	4.9	—	—	34.0
1952	62.9	19.0	5.04	2.4	2.8	7.8	31.6
1953	94.3	27.0	4.5	2.1	3.3	7.8	31.7
1954	124.5	29.0	3.4	1.7	4.1	7.6	34.8
1955	115.1	37.0	2.2	1.34	5.2	7.4	35.9
1956	155.0		2.6	1.33	4.1	7.0	35.9
1957	203·7		2.95	1.7	5.8	8.7	39.6
1958 Jan.-June			1.6	0.9	2.6	4.2	18.5

(1) Part (I) covering U.S.A., Latin America and Canada appeared in V. I, No. 1, p. 45 of this *Bulletin.*
(2) Part of the data obtained through courtesy of the British Council and the U.K. Trade Commissioner in India.
(3) For 1947, 1948 and 1949 the figures are for penicillin excluding ointments and liniments containing penicillin.

American pharmaceutical firms also have long established subsidiaries and sales office in U.K. In 1957 as much as 50 per cent of the drugs and medicinals sold to the NHS is reported to have come from these 'American' firms. Pfizers' sales branch in England was established in 1951 and manufacturing operations began two years later. In September 1955 the company's £2.5 million fermentation plant at Sandwich, Kent, was put on stream. This is Europe's largest plant for broad spectrum antibiotics, and Pfizers have plans to extend the laboratories and open new ones for production, control and fundamental research. After refining, the products are compounded into various pharmaceutical preparations in the company's Folkestone plant nearby which also began operations in 1955. Prior to 1955, Britain was importing Terramycin from U.S. Cyanamid of Great Britain (a subsidiary of American Cyanamid Co.) inaugurated in April this year a new, functionally built pharmaceutical plant at Gosport, Hants, to produce Aureomycin and Achromycin among other Lederle pharmaceuticals. This multi-million dollar project replaces the Hirwaun installation in South Wales which had been manufacturing Lederle pharmaceuticals since 1950.

The Upjohn Co. opened a London branch in 1953. Other American firms in U.K. are Abbott laboratories, Parke Davis, Squibb, Lilly, etc.

Exports.—In 1957 British exports of drugs and medicinals hit a record (£39.6 million), nearly three times the value in 1946. Antibiotics exports also reached a peak value, about 23 per cent (£ 9 million) of drug exports. In 1956, £7 million worth of antibiotics were exported, £1.33 million of which were from the sale of penicillin; this was less than the exports in 1955 by about £2,000, although the number of mega units sold was up by nearly 30 million. Receipts from other antibiotics fell from £5.22 in 1955 to £4.44 million in 1956. In recent years the value of export of pharmaceuticals has at least equalled the annual cost (about £35 million) of drugs supplied by chemists through NHS. India and Australia top the list of importers of British drugs. Although the volume of exports of penicillin and its preparations has steadily increased, the fall in their prices resulted in a decrease in value. However, this has nearly been made up by export of other antibiotics.

Imports.—Antibiotics imports into Britain.—

TABLE II

Antibiotics Imports into U.K.

Year	£
1954	4,800,000
1955	400,000
1956	781,962
1957	1,260,152

During the first six months of 1958 import of drugs and medicinal preparations made up of antibiotics, vitamins, etc., was £4.9 million compared to £4.1 million for the corresponding period in 1957.

Ireland and Scotland

Antigen Limited have opened a new antibiotic unit at Rosecrea, Co. Tipperary. Distillers Biochemicals of Glasgow are well known in the field. Glaxos have established a factory at Montrose.

Spain

Spain has made considerable progress in the past five years in the manufacture of antibiotics, in which the country is now almost self sufficient, imports being confined to the less common varieties. The industry has enlisted American technical know-how to a large extent and also works in close collaboration with some of the European antibiotic firms. The annual output of Spanish pharmaceuticals is now valued at \$50 million.

CEPA (Compania Espanola de Penicillina y Antibioticos, S.A.), the first and largest antibiotics plant, has a large fermentation unit at Aranjuez and a sterile packaging and formulating division just outside Madrid. Designed with Merck's assistance, the firm produces 100 billion units per month.

Antibioticos, S.A., another important company, has a penicillin plant at Leon working under licence from Schenley Laboratories of U.S.A. The Spanish government authorized expansion of both the above plants to meet the country's requirements of penicillin and also for production of streptomycin and other antibiotics on a large scale.

Farmabion, S.A., of Madrid, has a factory at Pamplona, established in collaboration with the Leo Pharmaceutical Co. of Copenhagen. The antibiotics plant set up by Spanish chemical manufacturers with Danish technical aid and initial capital of 50 million pesetas, commenced operations in 1957. It is to produce 7,000 kg. of penicillin initially, and other antibiotics later on.

Portugal

Antibiotics output in 1954 was valued at 20,000 contos, about 20% of the pharmaceuticals production valued at 119,030 contos. Development of the pharmaceutical industry, including manufacture of antibiotics and vitamins, is included in the second six-year plan of the Portuguese Government. Foreign firms have been invited to collaborate in and establish, local manufacture.

Italy

Concerted efforts at modernization and emphasis on highly scientific methods and personnel have made it possible for the Italian pharmaceutical industry to mass produce within the span of the last four or five years important antibiotics like penicillin and streptomycin (Industrie Chemiche Antibiotiche, Rome), tetracycline (Prodotti Lepetit Co., Milan), chlortetracycline (Alfar of Catalina) and Vulcamina, the sodium salt of novobiocin. Present annual output of the major antibiotics in Italy is estimated as: Penicillin and its preparations 50,000 B. units, streptomycin and dihydrostreptomycin 30 tons, chloramphenical 40 tons, tetracyline and chlortetracycline 10 tons. This production level has been maintained for the last three or four years in the case of penicillin, while the output of other antibiotics has progressively increased. Italian exports and imports of antibiotics is given in Table III.

Manufacture of synthetic chloramphenicol, was one of the biggest achievements of S. A. Farmaceutici Italia (Farmitalia) established nearly a quarter of a century ago and enjoying support of the "Montecatini" and "Rhone-Poulenc" groups. The company also has facilities for production of fermentation antibiotics. Farmitalia's plant at Settimo Torinese is among the finest of modern pharmaceutical factories in Europe and produces a comprehensive range of pharmaceuticals and intermediates, notably chloramphenicol, a range of penicillins, streptomycin, chlortetracycline, cycloserine, vitamin B_{12} and sulphonamides. Carlo Erba of Milan is another old and important manufacturing corcern producing a number of pharmaceuticals including antibiotics. Some of the Italian firms have now established subsidiaries in Latin America, Spain and Turkey.

Subsidiaries of American firms are also in operation in Italy. Parke, Davis and Co., formed an Italian subsidiary and established a branch office and manufacturing laboratory in Rome in 1956; the Parke, Davis Itali S.p.A., went into production in October 1956.

Chas. Pfizer's pharmaceutical plant near Latina, some forty miles southeast of Rome, was completed in 1957 to produce feed supplements among other Pfizer products.

TABLE III

Italy : Imports And Exports Of Antibiotics In Bulk 1, 2

Antibiotic	1955		1956		1957	
	Quantity	Value Rs.	Quantity	Value Rs.	Quantity	Value Rs.
Penicillin in Million i.u.						
Imports	163,083	87,275	338,221	387,375	1,133,800	953,983
Exports	8,207,937	2,375,334	3,266,260	897,783	2,940,660	1,266,167
Medicinal specialties containing penicillin						
Imports		2,623,567		926,192		231,925
Exports		4,008,258		4,248,750		2,606,308
Streptomycin in 100 kilos						
Imports	41.29	1,674,550	68.05	2,127,167	51.03	2,037,242
Exports	64.40	5,264,533	70.74	3,913,517	89.84	4,548,258
Medicinal specialties containing streptomycin						
Imports		262,883		433,625		546,945
Exports		2,829,292		4,526,192		3,217,167
Chloramphenicol in 100 kilos						
Imports	2.68	103,908	5.09	693,575	—	—
Exports	157.45	14,978,600	149.77	10,130,117	250.44	15,466,692
Medicinal specialties containing chloramphenicol						
Imports		1,142,933		492,133	—	—
Exports		7,440,450		5,896,558		7,030,558
Other antibiotics in 100 kilos						
Imports	20.40	1,921,058	53.79	10,586,558	49.51	6,343,775
Exports	1.20	509,508	13.17	1,759,092	19.20	2,791,858
Medicinal specialties containing other antibiotics						
Imports		7,556,783		7,541,208		5,248,483
Exports		271,767		2,447,475		5,161,308

(1) Courtesy: Farmitalia, Milan. (2) Conversion rate, Re. 1 = 120 lire.

Laboratori Palma, S.p.A., licensed manufacturers and distributors of Squibb pharmaceuticals including antibiotics and built under latter's technical supervision, opened new manufacturing laboratories in 1952.

Swiss firms like Ciba, Hoffmann-La Roche, Geigy and Sandoz have subsidiaries in Italy. Union Chimique de Belge and some West German, Dutch and British firms have interests in the Italian drug market.

Pharmaceuticals ($7.5 million) particularly antibiotics ($1 million), however, come mainly from U.S.A.

Italy exports pharmaceuticals, a greater part of which comprises of antibiotics, to

Mediterranean countries, Middle East, Far East and Central and South America.

TABLE IV.

Italy: Pharmaceuticals Imports and Exports

Year	Imports in million Rs.	Exports in million Rs.
1953	97.0	62.5
1954	107.5	86.6
1955	128.5	97.2
1956	170.0	100.4
1957	152.3	120.7

France

France has a well established antibiotic industry and is nearly self-sufficient even in some of the latest antibiotics. Large companies like the Rhône Poulenc are among the pioneers in the development of large-scale production of penicillin and dihydrostreptomycin. The firm has plants at Vitry-sur-Siene (pharmaceuticals), at Elbeuf (streptomycin, insecticides, etc.), and at other places and also markets the tetracyclines and spiramycin. Other important manufacturers are UCLAF producing framycetin, penicillin, streptomycin, etc., while Societe Antibiotique de France markets neomycin and bacitracin in addition to other common antibiotics.

Apart from these few big companies the pharmaceutical industry in France is divided among a large number of small enterprises engaged in making a narrow range of drugs or standard ones in limited quantity with the final stages of compounding being often left to retail pharmacists. For instance, in 1955 there were as many as 1300 manufacturers of pharmaceuticals, but one-third of the total turnover of £110 million came from six laboratories, while 50 laboratories together accounted for 80 per cent of the products. The French Health Ministry's regulations in respect of testing, certification and registration of drugs are stringent, and the number of competing drugs in a single category is also limited, so that when the Government register is full, manufacturers are pretty secure from new entrants. Exports and imports are also controlled by tight licencing regulations, the greater percentage of France's exports being to her overseas possessions. These factors have indirectly contributed to the country's self sufficiency in drugs. (*Pharm. J.* 180: 397, 1958).

American manufacturers have subsidiaries in France established in collaboration with local firms. In 1955 a Franco-American antibiotic plant was completed in Massey near Paris by the Societe Industrielle de Biochemie, with Chas. Pfizer of U.S. and the French Laboratories Clin-Comar (Societe d'Exploitation des Marques Clin-Byla) collaborating in the venture. The new plant produces Tetracin and Terramycin and eventually other antibiotics are to be taken up. Clin-Byla had been distributing Pfizer antibiotics in France since 1952.

Early this year Upjohn Co., and Societe Industrielle pour la Fabrication des Antibiotiques have jointly set up a 50 million francs pharmaceutical manufacturing concern. The new enterprise is named Union Chimique Atlantique.

Belgium

Belgium has a well developed antibiotics industry and exports penicillin, chloramphenicol, etc.

TABLE V.

Belgium: Antibiotics Exports and Imports, 1957[1]

Antibiotics	Exports		Imports	
	Quantity in 100 kg.	Value in 1000 Belg. francs.	Quantity in 100 kg.	Values in 1000 Belg. francs.
Penicillin and preparations	5,475	127,828	437	78,038
Chloramphenicol and preparations	36	18,977	69	46,534
Other antibiotics and preparations ..	5,382	406,108	4,664	513,126

(1) Courtesy: Federation des Industries Chimiques de Belgique, Bruxelles.

Antibiotics production is centered in the hands of Usines Recherche Industrie Therapeutique (R.I.T.) at Genval. The Belgo-Luxemburg Economic Union started manufacture of chlortetracycline in 1954.

Netherlands

The Dutch pharmaceutical industry is well established and has a high reputation. A range of drugs including penicillin, chloramphenicol, streptomycin and dihydrostreptomycin are exported. In the Gorcum factory (South Holland) the Central Sugar Co., Amsterdam planned production of streptomycin in co-operation with the Heyden Chemical Corporation of New York as far back as 1950. Production of this antibiotic and other pharmaceuticals commenced in 1954. Koninklijke Nederlandsche Gisten Spiriritusfabriek of Delft has been exporting penicillin since 1950.

Merck, Sharp and Dhome manufacturing unit opened at Haarlem in 1957 for supply of Merck pharmaceuticals to the European and Near East markets.

TABLE VI

Netherlands' Imports and Exports of Pharmaceuticals
(Value in 100 H.fl.)

Product	Import		Export	
	1955	1956	1955	1956
Penicillin ..	301	437	n.a.	n.a.
Antibiotics (undetermined)	515	424	n.a.	n.a.
Other antibiotics	2447	3119	243	1082
All pharmaceuticals ..	34820	47508	68941	91899

Denmark

The Danish pharmaceutical industry though comparatively young has made tremendous progress to more than quadruple the output since 1945. Over 70 per cent of the production is exported.

In 1952 at the Roskilde Medical Co., a fifty per cent cut in penicillin prices was made possible with Dr. Christensen's process of using slaughter house offals instead of corn-steep liquor in penicillin fermentation. In co-operation with the Co-operative Cheese Factory at Ringstead (Sea land) a new factory was put up in 1955 which obtains lactose from the cheese factory wastes for the production of penicillin.

There are no large manufacturing firms in Denmark. Of the two important antibiotics manufacturers the Leo Company of Copenhagen is the largest of its kind in Scandinavia, and has a modern, well designed factory producing a range of antibiotics, vitamins and hormones. The Novo Company, another fine factory, also produces antibiotics and other pharmaceuticals.

Pharmacy in general is state controlled. Goods and services of the highest standards only are tolerated. Advertisements of proprietary medicines are rare and only on the approval of the Board of Health. Hence, drugs listed in the Danish pharmacopoeia are in great demand.

Germany

In West Germany large scale penicillin production with a monthly output of 400,000

TABLE VII.

Denmark: Production, Imports and Exports of Pharmaceuticals
(Value in million Kr.)

Product	Production			Exports			Imports
	1950	1951	1953	1950	1951	1953	1953
Penicillin			45.7		29	41.4	3.5
Streptomycin						7.2	5.2
Pharmaceuticals	80	110		41	69		

mega units began in 1942 in Farbwerke Hoechst A.G. plant near Frankfurt. The firm produces streptomycin since 1954, and its Hostacyclin, a broad spectrum antibiotic is on the market since 1955, besides the penicillin-streptomycin combinations like Omnacillin and Omnamycin. Farbenfabriken Bayer A.G. at Leverkusen is another important manufacturer of pharmaceuticals including antibiotics.

C. F. Boehringer and Sohne GmbH., Mannheim-Waldorf are marketing synthetic chloramphenicol esters since 1956.

American firms with subsidiaries and sales facilities in operation in West Germany are Pfizer's plant (1954), while Squibb specialties including Nystatin are being marketed by Chemiche Fabrik von Heyden.

The pharmaceutical industry of the German Democratic Republic has been rebuilt after the war and antibiotics such as penicillin, chloramphenicol and Brevecid (A thermostable antibiotic from the mycelium of *P. notatum* for topical use) are now major products. Manufacture of oxytetracycline is planned for 1958. As early as 1950 the nationalized Schott Works in Jena was developed into a first class pharmaceutical factory to produce penicillin sufficient to cover domestic needs.

Germany is now exporting pharmaceuticals to European countries, South America and South Asia. Federal Germany's pharmaceutical exports in 1953, 1954 and 1955 were 9.1, 12.8, and 12.8 million DM respectively. Imports were up by 44 per cent for the whole of Germany in 1957.

Austria

In pre-war Austria there were few local pharmaceutical enterprises and as much as 80 per cent of the country's drug requirements had to be met by imports. Since 1945, 30 to 40 small firms have been set up, several of them operating under foreign licences. The industry has made such strides that the country's entire penicillin requirements and 75 per cent of the demands of other pharmaceuticals are now being met by home production.

Production of antibiotics is centered in the hands of Biochemie GmbH, with its main plant at Kundl, Tyrol. In the expansion programme of 1950 for the production of various salts of penicillin about one-third was earmarked for export. Biochemie developed Penicillin V with patent applications in 26 countries and a cross licence agreement with Eli Lilly Co. The firm also produces tyrothricin on a small scale. Streptomycin production was planned two years ago.

Switzerland

Although details of the various drugs and pharmaceuticals produced are not known, their turnover in 1956 in the four well known Swiss firms Ciba, Hoffman la Roche, Geigy and Sandoz, was valued at £80 million. Swiss firms import most of the raw materials while foreign sales account for most of the turnover. Ciba and Hoffman la Roche have extensive research projects in antibiotics isolation and development both at the parent company laboratories as well in a

TABLE VIII
Federal Germany. Production of Pharmaceuticals
(in million DM)

	1953	1954	1955	1956	1957
All pharmaceuticals	991.7	1,077.3	1,146.8	1,250	1,589
Pharm. chemicals	88.6	92.7	79.7		
Antibiotics	18.1	22.8	35.4		
Human pharm. specialities..	635.3	670.7	720.6		
Penicillin for retail sale	52.4	43.7	180.6		
Other pharm. specialities	582.9	626.96	702.5		

number of the overseas subsidiaries. Swiss pharmaceuticals are known for their high quality.

TABLE IX

Swiss: Export and Import of Pharmaceuticals

(in million S.fr.)

Year	Export	Import
1952	326,800	79,900
1953	357,500	86,700
1954	427,610	77,459
1955	454,106	95,443
1956	500,608	115,210
1957	600,700	

Norway

Local production of penicillin began in 1953 and the requirements of the country, estimated at 500 billion units annually, are met without importations. Prior to 1953 imports of the antibiotic was to the tune of £75,000 a year.

Sweden

Kabi and Co. produces oxytetracycline and tetracycline since 1955 under licence from Chas. Pfizer.

In 1946 the *Apotekarsocieten* arranged the pharmacies into groups by districts so that the larger pharmacies manufactured certain drugs and supplied the remainder of the group within the respective districts. Duplication was thus eliminated, small pharmacies were enabled to produce a variety of products, cost on capital expenditure, equipment and production was minimized and analytical control facilitated. The more difficult analyses are done in the Central Laboratory (A.K.L.)

TABLE X

Sweden: Production of Drugs

(in million Sw. Kr.)

Year	Value
1953	86.5
1954	95.0
1955	101.6

Drug exports in 1955 was valued at 18 million Sw. Kr. A fall in penicillin exports was noted in that year.

Finland

In 1956 a new Finnish lichen antibiotic of the tetracycline type was put on sale, first as a skin medicament, later to be tried for internal use. At present all other antibiotics are imported into Finland. There are seven important manufacturing firms in the country but a high percentage of the drugs sold and prescribed are foreign proprietaries.

* * *

U.S.A.—1957

Antibiotic	Production	Sales	Sale value in $1000
Penicillin in m.m. u.	528·9	455·7	66,345
Streptomycin in 1000 lbs.	198	169	6,786

A.N.

H. A. Notes

Company News

1957-58, A Year of All-Round Progress.—FINISHED PENICILLIN tested and passed was 21.43 million mega units compared to 9.90 million mega units in 1956-57. GROSS SALES amounted to Rs. 180.15 lakhs as against Rs. 57.80 lakhs in the previous year. GROSS SURPLUS available at the end of the year was Rs. 33.43 lakhs compared to Rs. 57,607 at the end of 1956-57. BETTER AMENITIES to the workers and their families were ensured with the provision of a hospital, welfare centre, kindergarten and co-operative consumers' stores.

Monetary Award.—In view of the record production and surplus achieved during 1957-58 and in appreciation of the hard work and co-operation extended by the employees, it has been decided to make a monetary award by way of ex-gratia payment. All employees of the Company drawing a basic pay of Rs. 500 and less will be paid one month's salary and allowances. To assist workers in the lower income group, a minimum of Rs. 125 and a maximum of Rs. 325 per head has been laid down. About Rs. 1 lakh will be disbursed under this scheme and over 95% of the staff would benefit. This award has created jubilation and enthusiasm among the employees.

Best Worker Annual Award.—Commencing from 1958-59 the "Best Workers" in the organization below the rank of chargeman Gr. II are to be recognized and awarded on 15th August every year. From each department names of three best workers will be submitted to the Works Committee which will screen the list and recommend to the Managing Director such persons who, in their opinion, merit the BEST WORKER AWARD. The first prize will be Rs. 100 in cash and the rest will receive certificates of merit.

More Penicillin Production.—During the first nine months of 1958 the quantity of finished penicillin tested and passed was 19.91 million mega units as against 10.8 million mega units for the corresponding period in 1957.

Higher Sales.—The gross sales for the first nine months of 1958 was Rs. 226.77 lakhs compared to Rs. 72.18 lakhs for the corresponding period in 1957.

Rossimycin.—A crystalline actinomycin type antibiotic isolated from culture filtrates of *Streptomyces chrysomallus* Lindenbein shows activity against gram positive bacteria and the acid fast organism *Mycobacterium phlei* at concentrations of 0.4 ug/ml. The Sloan Kettering Cancer Research Centre in New York reports that the antibiotic, like other actinomycins, has anticarcinogenic activity against ridgeway-osteosarcoma.

Waste Mycelium in Penicillin Fermentation.—Use of waste mycelia of *Penicillium chrysogenum* as one of the principal raw materials in penicillin fermentation is a very attractive economic proposition for a penicillin factory. Results of experiments carried out in shake flasks and 500 gallon fermentors under commercial production conditions show possibilities of such utilization of waste mycelia.

Ultrasonics in Strain Selection.—Ultrasonic treatment of an isolate from an original Russian strain of *Penicillium chrysogenum* (light brown spored) has yielded a new strain with 15 to 20 per cent higher penicillin production capacity than the

original strain under similar conditions. This is a co-operative project with the University of Poona.

Russian Experts.—The delegation of Soviet pharmaceutical experts headed by Mr. A. G. Natradze, presently touring India, visited the factory on 21st and 22nd August.

Public Accounts Committee.—The Public Accounts Committee visited the factory and stayed at Pimpri on 13th and 14th October.

Lectures.—Under the auspices of the science seminar, Mr. E. P. Moon, I.C.S., Adviser, Planning Commission, Government of India, gave a talk on "Industrial Planning" on 22nd August.

Prof. S. K. K. Jatkar, Head of the Department of Chemistry, Poona University, delivered on 1st September, the first of a series of lectures celebrating Kekule Valency Theory Centenary.

Another series of lectures celebrating the Darwin-Wallace Centenary is also being organized by the science seminar.

Going Abroad.—Dr. Kartar Singh of our Biochemistry Department was accorded a warm send-off on 19th August, prior to his departure to Ottawa, on a National Research Council of Canada post-doctoral fellowship.

Back Home.—Mr. B.V. Raman, our Superintendent Engineering, returned in the third week of September after a ten weeks' assignment in U.S.A. in connection with the expansion programme of the factory. He gave an interesting technical talk to the staff on what he saw in U.S.A.

* * *

Colony News

Independence Day.—15th of August was celebrated with the usual festivity. In the morning Shri S. T. Raja, Managing Director, hoisted the national flag in the factory and later at the Community and Welfare Centre, followed by distribution of sweets to children. A "mock parliament" was one of the highlights of the day's entertainment programme. In the evening Dr. D. G. Karve, well known economist, was the chief guest at a programme of music, dances and variety entertainment staged in the Welfare Centre auditorium.

Ganesh Chaturthi.—Commencing with the *pratishtapana* on 16th September the mahotsava provided a full five-day fare of entertainment, replete with drama, music, dances, film shows, magic shows, and a discourse by the noted scholar D. V. Potdar.

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Recognition of the Associateship Diploma of the Institution of Chemists (India) by examination :

In a recent office memorandum of the Ministry of Scientific Research and Cultural Affairs, the Government of India have decided that Associateship Diploma of the Institution of Chemists (India) by examination be recognised for all chemical appointments for which M.Sc. degree in Chemistry is prescribed as a qualification.

Edited by Dr. K. Ganapati and Published by Shantikumar T. Raja, B.A., LL.B. Bar-at-Law, Hindustan Antibiotics (Private) Ltd., Pimpri (near Poona). Printed by J. S. Pereira at the Examiner Press, Bombay—1.